I. PATENT ABSTRACTS OF JAPAN

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(54) SELECTIVE SEPARATION MEMBRANE

(57)Abstract:
PROBLEM TO BE SOLVED: To substantially prevent the elution of a hydrophilic high polymer recognized as foreign matters within the living body by specifying the content of the hydrophobic high polymer to be extracted by prescribed % of an aqueous ethanol solution into a selective separation membrane consisting of the hydrophilic high polymer and a hydrophobic high polymer to a prescribed value or below per prescribed area of the liquid to the treated contact side membrane of the selective separation membrane.
SOLUTION: The hydrophilic high polymer to be extracted by the 40% aqueous ethanol solution is ≤0 mg per 1 m2 the area of liquid to be treated contact side membrane of the selective separation membrane. The selective separation membrane is adequately usable in applications where inconvenience is induced by the elution of the hydrophilic high polymer; for example, thickening, refining, etc., of food, beverages and physiologically active materials in addition a blood purification. The water to be treated includes food, beverages and physiologically active material- containing liquids, etc. If the selective separation membrane is applied to the blood purification application to return the water to be treated again to the human body, safety is improved and, therefore, the membrane is most effective when the blood or the component of the blood is used as the water to be treated.

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CLAIMS

[Claim(s)]
[Claim 1] It sets to the selection demarcation membrane which consists of a hydrophobic macromolecule and a hydrophilic macromolecule, and is 40%. This hydrophilic macromolecule extracted in an ethanol water solution is 2 a processed liquid contact pleural membrane area of 1m of a selection demarcation membrane. Selection demarcation membrane characterized by being 10mg or less of hits.
[Claim 2] The selection demarcation membrane according to claim 1 whose processed liquid is blood.
[Claim 3] The selection demarcation membrane according to claim 1 or 2 used for the object for hemodialysis, the object for hemodialysis filtration, the object for hemofiltration, the object for plasma skimming, the object for plasma fractionation, or ascites concentration.
[Claim 4] The selection demarcation membrane according to claim 1 to 3 whose selection demarcation membrane is a hollow fiber.
[Claim 5] The selection demarcation membrane according to claim 1 to 4 whose hydrophobic macromolecule is polysulfone system resin.
[Claim 6] The selection demarcation membrane according to claim 1 to 5 whose hydrophilic giant molecule is a polyvinyl pyrrolidone.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] In the selection demarcation membrane which consists of a hydrophobic macromolecule and a hydrophilic macromolecule, this invention suppresses elution of this hydrophilic macromolecule, and relates to the selection demarcation membrane whose safety improved. Furthermore, when it uses for blood purification at a detail, it is related with the selection demarcation membrane containing the hydrophilic macromolecule whose safety improved by suppressing the elution to the blood of a hydrophilic macromolecule.
[0002]
[Description of the Prior Art] About a chronic-renal-failure patient's blood art, the living body kidney was made into the setmaster and the various improvement techniques in membraneous ability and the dialysis approach have been developed. As a film raw material used for them, natural raw materials, such as a cellulose and a cellulosic, and synthetic macromolecule raw materials, such as a polysulfone system, polymethylmethacrylate, a polyacrylonitrile, and an

ethylene-vinylalcohol copolymer, are used broadly. In the synthetic macromolecule raw material, it excels in biocompatibility, the polysulfone system resin which may discover the high clearance engine performance of the uremia matter attracts attention, and Kamiichi of many film for blood purification using polysulfone system resin is carried out in recent years. Polysulfone system resin is thermoplastic heat-resistant engineer plastics, and application expansion is broadly carried out in each industrial field.

[0003] Polysulfone system resin has comparatively strong hydrophobicity, and when it contacts blood, it tends to adsorb plasma protein. For this reason, in case the blood purification film is produced, in order to raise compatibility with blood, generally the approach of giving a hydrophilic property is used by mixing a polyvinyl pyrrolidone with polysulfone system resin.

[0004] It is known that critical side effects, such as an anaphylactic shock considered to originate in elution of a polyvinyl pyrrolidone during the hemodialysis therapy using the selection demarcation membrane containing a hydrophilic giant molecule, especially a polyvinyl pyrrolidone, will occur. Moreover, in Germany, there is regulation that the polyvinyl pyrrolidone more than K-18 (weight average molecular weight 10000) cannot be injected intravenously. Furthermore, it is reported by by injecting a polyvinyl pyrrolidone intravenously that an anaphylaxis symptom is shown (Pilar Maiques Asuero et al., The Annals of Pharmacotherapy, pp30, January, Vol.30, 1996). That is, the polyvinyl pyrrolidone generally used has a problem in safety as a hydrophilization agent of the polysulfone system resin film, and in case it uses for a blood purification application, it is necessary to suppress elution of the polyvinyl pyrrolidone to blood as much as possible.

[0005] In order to suppress elution of a polyvinyl pyrrolidone, the approach of the former many is proposed. For example, the method of suppressing elution of a polyvinyl pyrrolidone by constructing for it a bridge and insolubilizing a polyvinyl pyrrolidone is indicated by performing heat treatment or radiation processing for the polysulfone system hollow fiber containing a polyvinyl pyrrolidone to JP,10-230148,A. Moreover, the method of suppressing elution of a polyvinyl pyrrolidone is indicated by JP,10-243999,A by making thickness of a selection detached core suitable. However, although such technique is effective to the elution volume control to water or hot water, it is inadequate for elution volume control to 40% ethanol water solution used as the index of the elution volume to blood or plasma so that it may mention later. Also in the permeable membrane actually said to have controlled the elution volume of a polyvinyl pyrrolidone, the actual condition is having not solved the problem over the safety of the selection demarcation membrane which there is a report of anaphylactic shock generating (for example, Nakayama et al., O-439, the collection of the 43rd Japanese Society for Dialysis Therapy drafts, pp620, and 1998), and still contains a polyvinyl pyrrolidone.

[0006]

[Problem(s) to be Solved by the Invention] This invention aims at offering the selection demarcation membrane in which the hydrophilic macromolecule recognized to be a foreign matter in in the living body for the purpose of solving the above-mentioned technical problem cannot be eluted easily.

[0007]

[Means for Solving the Problem] These researchers reached this invention, as a result of inquiring wholeheartedly, in order to offer the selection demarcation membrane which solves the above-mentioned technical problem and possesses the outstanding safety. That is, this inventions are as follows.

** Set to the selection demarcation membrane which consists of a hydrophobic macromolecule

and a hydrophilic macromolecule, and it is 40%. This hydrophilic macromolecule extracted in an ethanol water solution is 2 a processed liquid contact pleural membrane area of 1m of a selection demarcation membrane. Selection demarcation membrane characterized by being 10mg or less of hits.

** The selection demarcation membrane given [above-mentioned] in ** a given processed liquid is blood.

** The above-mentioned ** used for the object for hemodialysis, the object for hemodialysis filtration, the object for hemofiltration, the object for plasma skimming, the object for plasma fractionation, or ascites concentration, or a selection demarcation membrane given in **.

** The above-mentioned ** whose selection demarcation membrane is a hollow fiber thru/or a selection demarcation membrane given in **.

** The above-mentioned ** whose hydrophobic macromolecule is polysulfone system resin thru/or a selection demarcation membrane given in **.

** The above-mentioned ** whose hydrophilic giant molecule is a polyvinyl pyrrolidone thru/or a selection demarcation membrane given in **.

[0008] The hydrophilic macromolecule extracted in an ethanol water solution 40% in this invention is 2 a processed liquid pleural membrane area of 1m of a selection demarcation membrane. It is based on the following reason that it is 10mg or less of hits. First, in the selection demarcation membrane which consists of a hydrophobic macromolecule and a hydrophilic macromolecule, since it was impossible to have made elution of this hydrophilic macromolecule there be nothing, the upper limit of safety needed to be decided. Although it changed with people, when the anaphylactic reaction when we inject a polyvinyl pyrrolidone intravenously using a beagle was investigated, as for the allergic response to the eluted polyvinyl pyrrolidone, it turned out that intravenous injection of a 5mg [per weight of 1kg] polyvinyl pyrrolidone does not cause an anaphylactic reaction. the upper limit of the film surface product of the dialyzer which considers people's solid-state difference, and makes an upper limit 1/10 of the insurance doses of a beagle, and is usually used for hemodialysis -- about 2 -- m2 it is -- if the minimum of the weight of things and a dialysis patient is set to 40kg -- 20mg per 1 dialysis -- the administration upper limit of a polyvinyl pyrrolidone -- it is -- 1m2 per -- it is thought that safety is securable by being referred to as 10mg or less.

[0009] When we actually measured the elution volume of the polyvinyl pyrrolidone by extract trial with 40% ethanol water solution of the polysulfone system permeable membrane containing the polyvinyl pyrrolidone by which current marketing is carried out, it is 2 1m. It turned out that there is elution of a 10mg - hundreds of mg hit number. Therefore, in order to secure the safety of the polysulfone system film containing a polyvinyl pyrrolidone, it is 2 1m by these data. It can attain by holding down to the elution volume of 10mg or less of hits.

[0010] Moreover, the reason we chose the extract by the ethanol water solution 40% is based on below. That is, when using a selection demarcation membrane for the object of blood purification, a processed liquid is not water but blood, or plasma. Since blood or plasma contains the organic component of an electrolyte, plasma protein, a corpuscle, and others in water, the solvent power over various solutes is said to be quite high compared with water or hot water. It is said that the extract by 40% ethanol water solution is used for measurement of the sampling volume of the additive (phthalic ester) of a vinyl chloride used for blood circuits, and has the extract force more near blood compared with water or hot water. I thought that the elution volume of the polyvinyl pyrrolidone at the time of blood contact of the selection demarcation membrane containing a polyvinyl pyrrolidone could be measured by using an ethanol water

solution this 40%.
[0011] When we actually measured the polyvinyl-pyrrolidone elution volume of current and the selection demarcation membrane containing a polyvinyl pyrrolidone marketed with 70-degree-C pure water in the ethanol water solution 40% as other conditions being the same, it turned out that the sampling volume by 40% ethanol water solution will be 5 to 20 times the sampling volume of 70-degree-C pure water.
[0012] This hydrophilic macromolecule extracted in an ethanol water solution 40% by the above research is 2 a processed liquid pleural membrane area of 1m of this selection demarcation membrane. A header and this invention were reached [that the selection demarcation membrane whose safety improved remarkably is obtained, and] by making it 10mg or less of hits.
[0013] In this invention, a processed liquid means the liquid which serves as an object for separation by the selection demarcation membrane, and a processed liquid contact side says the near front face where a membranous processed liquid contacts. That is, in hemodialysis, hemofiltration, hemodialysis filtration, and plasma skimming, a processed liquid is blood, a processed liquid is plasma in plasma fractionation, and a processed liquid contact side means the membranous blood (in the case of plasma fractionation, it is plasma) contact surface in this case. When the selection demarcation membrane of a hollow filament configuration is used for a blood purification application, a processed liquid contact side is usually the hollow filament inside. In hemodialysis or hemodialysis filtration, although blood is poured in membranous one side and dialysing fluid is poured to an opposite hand, in this invention, a processed liquid is blood or a constituent of blood, and, in such a case, is not dialysing fluid by suppressing elution of a hydrophilic macromolecule from the film to a processed liquid, so that clearly from the object which improves safety.
[0014] Moreover, although this invention can be used by a hydrophilic macromolecule besides blood purification being eluted suitable for concentration, purification, etc. of the application which inconvenience produces, for example, food and a drink, and a physiological active substance and food, a drink, a physiological active substance content liquid, etc. can be mentioned as a processed liquid This invention is the most effective, when applying this invention to the blood purification application which returns a processed liquid to the body again and the component of blood or blood is used as a processed liquid, since safety improves. It is desirable to apply to the blood purification application which returns the blood after processing to the body as mentioned above, the hemodialysis film, a hemodialysis filtration membrane, a blood filtration membrane, a plasma demarcation membrane, the plasma fractionation film, the ascites concentration film, etc. specifically mention, and the selection demarcation membrane of this invention is ****. As a gestalt which the selection demarcation membrane of this invention can take, although a flat film, the tubular film, a hollow fiber, etc. are mentioned, the hollow fiber which can take the large film surface product per unit volume is desirable.
[0015] Although the hydrophobic giant molecule in this invention has cellulose type raw materials, such as synthetic macromolecules, such as polyester, a polycarbonate, polyurethane, a polyamide, polysulfone, polyether sulphone, and polymethylmethacrylate, and cellulose triacetate, nitrocellulose, and is not limited especially, polysulfone system raw materials, such as polysulfone and polyether sulphone, are desirable [a giant molecule], since it excels in biocompatibility and the high clearance engine performance of the uremia matter is obtained, when it is used for blood purification. Moreover, these may be used independently, or may mix and use two or more sorts.
[0016] Although the hydrophilic giant molecules in this invention are raw materials, such as a

polyethylene glycol, polyvinyl alcohol, a polyvinyl pyrrolidone, a carboxymethyl cellulose, starch and its derivative, and cellulose acetate, a polyvinyl pyrrolidone is desirable from having compatibility with polysulfone system resin.

[0017] As an operation gestalt of this invention, the molecular weight of a hydrophilic macromolecule is the most important. In the film which consists of polysulfone system resin and a polyvinyl pyrrolidone, it is thought that a polyvinyl pyrrolidone is enclosed by polysulfone system resin and exists. Therefore, it is hard coming to fall out by enlarging molecular weight of a hydrophilic macromolecule out of the film. As for the polyvinyl pyrrolidone, different grade of molecular weight is marketed, and number average molecular weight cannot consider easily that are about about 360,000 and the polyvinyl pyrrolidone of molecular weight of this amount falls out out of the film for the grade (K-90) with the largest molecular weight. However, it has commercial polyvinyl-pyrrolidone molecular weight distribution, and the about 10,000 to 100,000 molecular weight number molecule is contained so much. In our examination result, when the eluted polyvinyl pyrrolidone was measured with gel permeation chromatography by extract experiment with 40% ethanol water solution of the polysulfone system resin film produced using K-90, the molecular weight is two to about 50,000, and most of the polyvinyl pyrrolidone of 100,000 or more molecular weight was not detected. That is, although approaches, such as chromatography and the reprecipitating method, are not asked, it becomes possible by using it, in case a measure is taken to commercial Polyvinylpyrrolidone K90, a low-molecular-weight object is removed positively and hollow fiber film production of this is carried out to suppress elution of the polyvinyl pyrrolidone by ethanol water-solution extract to 10mg or less per two a processed liquid contact pleural membrane area of 1m 40%. The low-molecular-weight object removed is usually less than 100,000 preferably less than 50,000 molecular weight.

[0018] An example shows the detail of this invention below.

[0019] The following procedures performed the ethanol extract trial 40%. After pouring the pure water of 400mL(s) inside [hollow filament] the hollow fiber module (processed liquid side) and doing the Flushing activity on it, the 40vol(s) % ethanol water solution permuted the hollow filament inside for the pure water in a module. The inside of the module case of a hollow filament outside was also filled with 40vol(s) % ethanol, and was closed. Next, after circulating flow rate 150 mL/min, 40 degrees C, and the 1-hour hollow filament inside for the 40vol(s) % ethanol water solution of 200mL(s), the polyvinyl-pyrrolidone concentration in the 40vol(s) % ethanol water solution through which it circulated was measured. They are 200mL(s) in the modular hollow filament inside volume and the volume for a header of a module inlet-port outlet, i.e., priming volume. The extracted polyvinyl-pyrrolidone weight is found from the applied polyvinyl-pyrrolidone concentration in the whole extract product and an extract, and the polyvinyl-pyrrolidone sampling volume per two is further calculated a processed liquid contact pleural membrane area of 1m from the film surface product (hollow filament bore criteria) of a hollow fiber module.

[0020] The approach of KMueller (1968) was used for the density measurement of a polyvinyl pyrrolidone. That is, a citric acid and iodine liquid were added to the specimen, the absorbance was measured, and it asked for concentration by the calibration curve searched for from Polyvinylpyrrolidone K90. In the case of density measurement, in order to lose inhibition of coloring by ethanol, it is necessary to dilute here more than twice. When it was specifically two fold serial dilution, after often mixing 1.25mL(s), water 1.25mL, 0.2M citric-acid water-solution 1.25mL, and 0.006N iodine water-solution 0.5mL and putting a specimen (a preparation or extract) for 10 minutes, the absorbance in 470nm was measured and the concentration of a

polyvinyl pyrrolidone was measured.
[0021]
[Example]
[0022] Example 1 polyvinyl-pyrrolidone (K-90, BASF A.G. make) 0.025g/mL A bath ratio [as opposed to the water of a water solution for a water solution] is 2.5-3.0. It is the polyvinyl pyrrolidone which trickled into the acetone which is the poor solvent which is twice, and removed the low-molecular-weight object positively by the reprecipitating method 90% of yield It obtained. This is hereafter called a purification polyvinyl pyrrolidone. The profile of the polyvinyl pyrrolidone before purification and the gel permeation chromatography of the fractionation eliminated at the time of purification is shown in drawing 1 and drawing 2 . It turns out that only low-molecular fractionation (direction where transparency time amount is long) is selectively eliminated at the time of purification so that more clearly than drawing. The dimethylacetamide 74 weight section and the water 5 weight section for the polyether sulphone (4800P, Sumitomo Chemical Co., Ltd. make) 16 weight section and the purification polyvinyl-pyrrolidone 5 weight section as the mixed dissolution and a spinning undiluted solution which carried out degassing The dimethylacetamide water solution was used as core liquid 50%, this was drawn into 75 degrees C and the coagulation bath of water through discharge and the 50cm free-running section from the double pipe orifice, the hollow fiber was formed, it wound after rinsing, and 20hr desiccation was carried out at 60 degrees C. The module of 2 was obtained 1.5m of hollow filament bore criteria film surface products using this hollow fiber. As a result of this module's performing an ethanol extract trial 40%, elution of a polyvinyl pyrrolidone is 2 a hollow filament intima area of 1m. It was 1.0mg of hits.
[0023] The example 2 polysulfone (P-1700, product made from AMOCO) 20 weight section, the purification polyvinyl-pyrrolidone 6 weight section, and the dimethylacetamide 74 weight section were used as the mixed dissolution and a spinning undiluted solution which carried out degassing, the dimethylacetamide water solution was used as core liquid 45%, this was drawn into 50 degrees C and the coagulation bath of water through discharge and the 70cm free-running section from the double pipe orifice, the hollow fiber was formed, it wound after rinsing, and 20hr desiccation was carried out at 60 degrees C. The module of 2 was obtained 1.5m of hollow filament bore criteria film surface products using this hollow filament. As a result of this module's performing an ethanol extract trial 40%, elution of a polyvinyl pyrrolidone is 2 a hollow filament intima area of 1m. It was 1.3mg of hits.
[0024] Except having used K-90 (BASF A.G. make) which is not refined as an example polyvinyl pyrrolidone of a comparison, like the example 2, spinning of the hollow fiber was carried out and the module of 2 was obtained 1.5m of hollow filament bore criteria film surface products using the obtained hollow filament. As a result of this module's performing an ethanol extract trial 40%, elution of a polyvinyl pyrrolidone is 2 a hollow filament intima area of 1m. It was 15.2mg of hits.
[0025]
[A table 1]

	実施例1	実施例2	比較例
親水性高分子の溶出量(mg)	1．0	1．3	15．2

[0026]
[Effect of the Invention] By this invention, although the hydrophilic macromolecule was contained, the selection demarcation membrane with little elution of this hydrophilic

macromolecule was able to be offered.

TECHNICAL FIELD

[Field of the Invention] In the selection demarcation membrane which consists of a hydrophobic macromolecule and a hydrophilic macromolecule, this invention suppresses elution of this hydrophilic macromolecule, and relates to the selection demarcation membrane whose safety improved. Furthermore, when it uses for blood purification at a detail, it is related with the selection demarcation membrane containing the hydrophilic macromolecule whose safety improved by suppressing the elution to the blood of a hydrophilic macromolecule.

PRIOR ART

[Description of the Prior Art] About a chronic-renal-failure patient's blood art, the living body kidney was made into the setmaster and the various improvement techniques in membraneous ability and the dialysis approach have been developed. As a film raw material used for them, natural raw materials, such as a cellulose and a cellulosic, and synthetic macromolecule raw materials, such as a polysulfone system, polymethylmethacrylate, a polyacrylonitrile, and an ethylene-vinylalcohol copolymer, are used broadly. In the synthetic macromolecule raw material, it excels in biocompatibility, the polysulfone system resin which may discover the high clearance engine performance of the uremia matter attracts attention, and Kamiichi of many film for blood purification using polysulfone system resin is carried out in recent years. Polysulfone system resin is thermoplastic heat-resistant engineer plastics, and application expansion is broadly carried out in each industrial field.

[0003] Polysulfone system resin has comparatively strong hydrophobicity, and when it contacts blood, it tends to adsorb plasma protein. For this reason, in case the blood purification film is produced, in order to raise compatibility with blood, generally the approach of giving a hydrophilic property is used by mixing a polyvinyl pyrrolidone with polysulfone system resin.

[0004] It is known that critical side effects, such as an anaphylactic shock considered to originate in elution of a polyvinyl pyrrolidone during the hemodialysis therapy using the selection demarcation membrane containing a hydrophilic giant molecule, especially a polyvinyl pyrrolidone, will occur. Moreover, in Germany, there is regulation that the polyvinyl pyrrolidone more than K-18 (weight average molecular weight 10000) cannot be injected intravenously. Furthermore, it is reported by by injecting a polyvinyl pyrrolidone intravenously that an anaphylaxis symptom is shown (Pilar Maiques Asuero et al., The Annals of Pharmacotherapy, pp30, January, Vol.30, 1996). That is, the polyvinyl pyrrolidone generally used has a problem in safety as a hydrophilization agent of the polysulfone system resin film, and in case it uses for a blood purification application, it is necessary to suppress elution of the polyvinyl pyrrolidone to blood as much as possible.

[0005] In order to suppress elution of a polyvinyl pyrrolidone, the approach of the former many is proposed. For example, the method of suppressing elution of a polyvinyl pyrrolidone by constructing for it a bridge and insolubilizing a polyvinyl pyrrolidone is indicated by performing heat treatment or radiation processing for the polysulfone system hollow fiber containing a polyvinyl pyrrolidone to JP,10-230148,A. Moreover, the method of suppressing elution of a

polyvinyl pyrrolidone is indicated by JP,10-243999,A by making thickness of a selection detached core suitable. However, although such technique is effective to the elution volume control to water or hot water, it is inadequate for elution volume control to 40% ethanol water solution used as the index of the elution volume to blood or plasma so that it may mention later. Also in the permeable membrane actually said to have controlled the elution volume of a polyvinyl pyrrolidone, the actual condition is having not solved the problem over the safety of the selection demarcation membrane which there is a report of anaphylactic shock generating (for example, Nakayama et al., O-439, the collection of the 43rd Japanese Society for Dialysis Therapy drafts, pp620, and 1998), and still contains a polyvinyl pyrrolidone.

EFFECT OF THE INVENTION

[Effect of the Invention] By this invention, although the hydrophilic macromolecule was contained, the selection demarcation membrane with little elution of this hydrophilic macromolecule was able to be offered.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention aims at offering the selection demarcation membrane in which the hydrophilic macromolecule recognized to be a foreign matter in in the living body for the purpose of solving the above-mentioned technical problem cannot be eluted easily.

MEANS

[Means for Solving the Problem] These researchers reached this invention, as a result of inquiring wholeheartedly, in order to offer the selection demarcation membrane which solves the above-mentioned technical problem and possesses the outstanding safety. That is, this inventions are as follows.

** Set to the selection demarcation membrane which consists of a hydrophobic macromolecule and a hydrophilic macromolecule, and it is 40%. This hydrophilic macromolecule extracted in an ethanol water solution is 2 a processed liquid contact pleural membrane area of 1m of a selection demarcation membrane. Selection demarcation membrane characterized by being 10mg or less of hits.

** The selection demarcation membrane given [above-mentioned] in ** a given processed liquid is blood.

** The above-mentioned ** used for the object for hemodialysis, the object for hemodialysis filtration, the object for hemofiltration, the object for plasma skimming, the object for plasma fractionation, or ascites concentration, or a selection demarcation membrane given in **.

** The above-mentioned ** whose selection demarcation membrane is a hollow fiber thru/or a selection demarcation membrane given in **.

** The above-mentioned ** whose hydrophobic macromolecule is polysulfone system resin thru/or a selection demarcation membrane given in **.

** The above-mentioned ** whose hydrophilic giant molecule is a polyvinyl pyrrolidone thru/or a selection demarcation membrane given in **.

[0008] The hydrophilic macromolecule extracted in an ethanol water solution 40% in this invention is 2 a processed liquid pleural membrane area of 1m of a selection demarcation membrane. It is based on the following reason that it is 10mg or less of hits. First, in the selection demarcation membrane which consists of a hydrophobic macromolecule and a hydrophilic macromolecule, since it was impossible to have made elution of this hydrophilic macromolecule there be nothing, the upper limit of safety needed to be decided. Although it changed with people, when the anaphylactic reaction when we inject a polyvinyl pyrrolidone intravenously using a beagle was investigated, as for the allergic response to the eluted polyvinyl pyrrolidone, it turned out that intravenous injection of a 5mg [per weight of 1kg] polyvinyl pyrrolidone does not cause an anaphylactic reaction. the upper limit of the film surface product of the dialyzer which considers people's solid-state difference, and makes an upper limit 1/10 of the insurance doses of a beagle, and is usually used for hemodialysis -- about 2 -- m2 it is -- if the minimum of the weight of things and a dialysis patient is set to 40kg -- 20mg per 1 dialysis -- the administration upper limit of a polyvinyl pyrrolidone -- it is -- 1m2 per -- it is thought that safety is securable by being referred to as 10mg or less.

[0009] When we actually measured the elution volume of the polyvinyl pyrrolidone by extract trial with 40% ethanol water solution of the polysulfone system permeable membrane containing the polyvinyl pyrrolidone by which current marketing is carried out, it is 2 1m. It turned out that there is elution of a 10mg - hundreds of mg hit number. Therefore, in order to secure the safety of the polysulfone system film containing a polyvinyl pyrrolidone, it is 2 1m by these data. It can attain by holding down to the elution volume of 10mg or less of hits.

[0010] Moreover, the reason we chose the extract by the ethanol water solution 40% is based on below. That is, when using a selection demarcation membrane for the object of blood purification, a processed liquid is not water but blood, or plasma. Since blood or plasma contains the organic component of an electrolyte, plasma protein, a corpuscle, and others in water, the solvent power over various solutes is said to be quite high compared with water or hot water. It is said that the extract by 40% ethanol water solution is used for measurement of the sampling volume of the additive (phthalic ester) of a vinyl chloride used for blood circuits, and has the extract force more near blood compared with water or hot water. I thought that the elution volume of the polyvinyl pyrrolidone at the time of blood contact of the selection demarcation membrane containing a polyvinyl pyrrolidone could be measured by using an ethanol water solution this 40%.

[0011] When we actually measured the polyvinyl-pyrrolidone elution volume of current and the selection demarcation membrane containing a polyvinyl pyrrolidone marketed with 70-degree-C pure water in the ethanol water solution 40% as other conditions being the same, it turned out that the sampling volume by 40% ethanol water solution will be 5 to 20 times the sampling volume of 70-degree-C pure water.

[0012] This hydrophilic macromolecule extracted in an ethanol water solution 40% by the above research is 2 a processed liquid pleural membrane area of 1m of this selection demarcation membrane. A header and this invention were reached [that the selection demarcation membrane whose safety improved remarkably is obtained, and] by making it 10mg or less of hits.

[0013] In this invention, a processed liquid means the liquid which serves as an object for separation by the selection demarcation membrane, and a processed liquid contact side says the near front face where a membranous processed liquid contacts. That is, in hemodialysis,

hemofiltration, hemodialysis filtration, and plasma skimming, a processed liquid is blood, a processed liquid is plasma in plasma fractionation, and a processed liquid contact side means the membranous blood (in the case of plasma fractionation, it is plasma) contact surface in this case. When the selection demarcation membrane of a hollow filament configuration is used for a blood purification application, a processed liquid contact side is usually the hollow filament inside. In hemodialysis or hemodialysis filtration, although blood is poured in membranous one side and dialysing fluid is poured to an opposite hand, in this invention, a processed liquid is blood or a constituent of blood, and, in such a case, is not dialysing fluid by suppressing elution of a hydrophilic macromolecule from the film to a processed liquid, so that clearly from the object which improves safety.

[0014] Moreover, although this invention can be used by a hydrophilic macromolecule besides blood purification being eluted suitable for concentration, purification, etc. of the application which inconvenience produces, for example, food and a drink, and a physiological active substance and food, a drink, a physiological active substance content liquid, etc. can be mentioned as a processed liquid This invention is the most effective, when applying this invention to the blood purification application which returns a processed liquid to the body again and the component of blood or blood is used as a processed liquid, since safety improves. It is desirable to apply to the blood purification application which returns the blood after processing to the body as mentioned above, the hemodialysis film, a hemodialysis filtration membrane, a blood filtration membrane, a plasma demarcation membrane, the plasma fractionation film, the ascites concentration film, etc. specifically mention, and the selection demarcation membrane of this invention is ****. As a gestalt which the selection demarcation membrane of this invention can take, although a flat film, the tubular film, a hollow fiber, etc. are mentioned, the hollow fiber which can take the large film surface product per unit volume is desirable.

[0015] Although the hydrophobic giant molecule in this invention has cellulose type raw materials, such as synthetic macromolecules, such as polyester, a polycarbonate, polyurethane, a polyamide, polysulfone, polyether sulphone, and polymethylmethacrylate, and cellulose triacetate, nitrocellulose, and is not limited especially, polysulfone system raw materials, such as polysulfone and polyether sulphone, are desirable [a giant molecule], since it excels in biocompatibility and the high clearance engine performance of the uremia matter is obtained, when it is used for blood purification. Moreover, these may be used independently, or may mix and use two or more sorts.

[0016] Although the hydrophilic giant molecules in this invention are raw materials, such as a polyethylene glycol, polyvinyl alcohol, a polyvinyl pyrrolidone, a carboxymethyl cellulose, starch and its derivative, and cellulose acetate, a polyvinyl pyrrolidone is desirable from having compatibility with polysulfone system resin.

[0017] As an operation gestalt of this invention, the molecular weight of a hydrophilic macromolecule is the most important. In the film which consists of polysulfone system resin and a polyvinyl pyrrolidone, it is thought that a polyvinyl pyrrolidone is enclosed by polysulfone system resin and exists. Therefore, it is hard coming to fall out by enlarging molecular weight of a hydrophilic macromolecule out of the film. As for the polyvinyl pyrrolidone, different grade of molecular weight is marketed, and number average molecular weight cannot consider easily that are about about 360,000 and the polyvinyl pyrrolidone of molecular weight of this amount falls out out of the film for the grade (K-90) with the largest molecular weight. However, it has commercial polyvinyl-pyrrolidone molecular weight distribution, and the about 10,000 to 100,000 molecular weight number molecule is contained so much. In our examination result,

when the eluted polyvinyl pyrrolidone was measured with gel permeation chromatography by extract experiment with 40% ethanol water solution of the polysulfone system resin film produced using K-90, the molecular weight is two to about 50,000, and most of the polyvinyl pyrrolidone of 100,000 or more molecular weight was not detected. That is, although approaches, such as chromatography and the reprecipitating method, are not asked, it becomes possible by using it, in case a measure is taken to commercial Polyvinylpyrrolidone K90, a low-molecular-weight object is removed positively and hollow fiber film production of this is carried out to suppress elution of the polyvinyl pyrrolidone by ethanol water-solution extract to 10mg or less per two a processed liquid contact pleural membrane area of 1m 40%. The low-molecular-weight object removed is usually less than 100,000 preferably less than 50,000 molecular weight.

[0018] An example shows the detail of this invention below.

[0019] The following procedures performed the ethanol extract trial 40%. After pouring the pure water of 400mL(s) inside [hollow filament] the hollow fiber module (processed liquid side) and doing the Flushing activity on it, the 40vol(s) % ethanol water solution permuted the hollow filament inside for the pure water in a module. The inside of the module case of a hollow filament outside was also filled with 40vol(s) % ethanol, and was closed. Next, after circulating flow rate 150 mL/min, 40 degrees C, and the 1-hour hollow filament inside for the 40vol(s) % ethanol water solution of 200mL(s), the polyvinyl-pyrrolidone concentration in the 40vol(s) % ethanol water solution through which it circulated was measured. They are 200mL(s) in the modular hollow filament inside volume and the volume for a header of a module inlet-port outlet, i.e., priming volume. The extracted polyvinyl-pyrrolidone weight is found from the applied polyvinyl-pyrrolidone concentration in the whole extract product and an extract, and the polyvinyl-pyrrolidone sampling volume per two is further calculated a processed liquid contact pleural membrane area of 1m from the film surface product (hollow filament bore criteria) of a hollow fiber module.

[0020] The approach of KMueller (1968) was used for the density measurement of a polyvinyl pyrrolidone. That is, a citric acid and iodine liquid were added to the specimen, the absorbance was measured, and it asked for concentration by the calibration curve searched for from Polyvinylpyrrolidone K90. In the case of density measurement, in order to lose inhibition of coloring by ethanol, it is necessary to dilute here more than twice. When it was specifically two fold serial dilution, after often mixing 1.25mL(s), water 1.25mL, 0.2M citric-acid water-solution 1.25mL, and 0.006N iodine water-solution 0.5mL and putting a specimen (a preparation or extract) for 10 minutes, the absorbance in 470nm was measured and the concentration of a polyvinyl pyrrolidone was measured.

EXAMPLE

[Example]

[0022] Example 1 polyvinyl-pyrrolidone (K-90, BASF A.G. make) 0.025g/mL A bath ratio [as opposed to the water of a water solution for a water solution] is 2.5-3.0. It is the polyvinyl pyrrolidone which trickled into the acetone which is the poor solvent which is twice, and removed the low-molecular-weight object positively by the reprecipitating method 90% of yield It obtained. This is hereafter called a purification polyvinyl pyrrolidone. The profile of the polyvinyl pyrrolidone before purification and the gel permeation chromatography of the fractionation eliminated at the time of purification is shown in drawing 1 and drawing 2 . It turns

out that only low-molecular fractionation (direction where transparency time amount is long) is selectively eliminated at the time of purification so that more clearly than drawing. The dimethylacetamide 74 weight section and the water 5 weight section for the polyether sulphone (4800P, Sumitomo Chemical Co., Ltd. make) 16 weight section and the purification polyvinyl-pyrrolidone 5 weight section as the mixed dissolution and a spinning undiluted solution which carried out degassing The dimethylacetamide water solution was used as core liquid 50%, this was drawn into 75 degrees C and the coagulation bath of water through discharge and the 50cm free-running section from the double pipe orifice, the hollow fiber was formed, it wound after rinsing, and 20hr desiccation was carried out at 60 degrees C. The module of 2 was obtained 1.5m of hollow filament bore criteria film surface products using this hollow fiber. As a result of this module's performing an ethanol extract trial 40%, elution of a polyvinyl pyrrolidone is 2 a hollow filament intima area of 1m. It was 1.0mg of hits.

[0023] The example 2 polysulfone (P-1700, product made from AMOCO) 20 weight section, the purification polyvinyl-pyrrolidone 6 weight section, and the dimethylacetamide 74 weight section were used as the mixed dissolution and a spinning undiluted solution which carried out degassing, the dimethylacetamide water solution was used as core liquid 45%, this was drawn into 50 degrees C and the coagulation bath of water through discharge and the 70cm free-running section from the double pipe orifice, the hollow fiber was formed, it wound after rinsing, and 20hr desiccation was carried out at 60 degrees C. The module of 2 was obtained 1.5m of hollow filament bore criteria film surface products using this hollow filament. As a result of this module's performing an ethanol extract trial 40%, elution of a polyvinyl pyrrolidone is 2 a hollow filament intima area of 1m. It was 1.3mg of hits.

[0024] Except having used K-90 (BASF A.G. make) which is not refined as an example polyvinyl pyrrolidone of a comparison, like the example 2, spinning of the hollow fiber was carried out and the module of 2 was obtained 1.5m of hollow filament bore criteria film surface products using the obtained hollow filament. As a result of this module's performing an ethanol extract trial 40%, elution of a polyvinyl pyrrolidone is 2 a hollow filament intima area of 1m. It was 15.2mg of hits.

[0025]

[A table 1]

	実施例1	実施例2	比較例
親水性高分子の溶出量(mg)	1．0	1．3	15．2

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

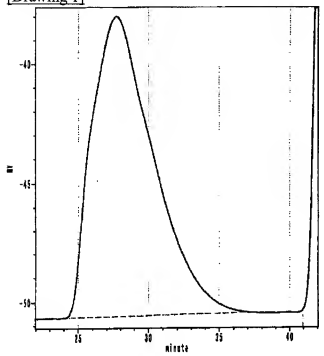
[Drawing 1] The profile of the gel permeation chromatography of a polyvinyl pyrrolidone (K-90) is shown.

[Drawing 2] The profile of the gel permeation chromatography of the fractionation eliminated at the time of polyvinyl-pyrrolidone purification is shown.

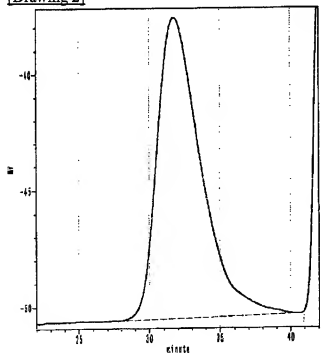
[Drawing 3] The profile of the gel permeation chromatography of a polyvinyl pyrrolidone by which elution was detected by ethanol extract 40% is shown.

DRAWINGS

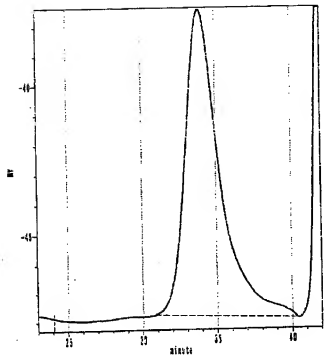
[Drawing 1]



[Drawing 2]



[Drawing 3]



[Translation done.]

50-71

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最終頁に続く

(54)【発明の名称】　選択分離膜

(57)【要約】
【課題】親水性高分子を含有する選択分離膜において、被処理液接触側からの該親水性高分子の溶出を抑え、安全性が向上した選択分離膜を提供する。
【解決手段】40% エタノール水溶液で抽出される親水性高分子が選択分離膜の被処理液接触側面積1m^2 あたり10mg以下であることを特徴とする選択分離膜。

【特許請求の範囲】

【請求項１】　疎水性高分子と親水性高分子からなる選択分離膜において、40% エタノール水溶液で抽出される該親水性高分子が選択分離膜の被処理液接触側膜面積1m^2 あたり10mg以下であることを特徴とする選択分離膜。

【請求項２】　被処理液が血液である請求項１記載の選択分離膜。

【請求項３】　血液透析用、血液透析濾過用、血液濾過用、血漿分離用、血漿分画用または腹水濃縮用に用いる請求項１または２記載の選択分離膜。

【請求項４】　選択分離膜が中空糸膜である請求項１乃至３記載の選択分離膜。

【請求項５】　疎水性高分子がポリスルホン系樹脂である請求項１乃至４記載の選択分離膜。

【請求項６】親水性高分子がポリビニルピロリドンである請求項１乃至５記載の選択分離膜。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、疎水性高分子と親水性高分子からなる選択分離膜において、該親水性高分子の溶出を抑え、安全性が向上した選択分離膜に関する。さらに詳細には、血液浄化に用いた際、親水性高分子の血液への溶出を抑えることにより、安全性が向上した親水性高分子を含有する選択分離膜に関する。

【０００２】

【従来の技術】慢性腎不全患者の血液処理方法については、生体腎を模範とし、種々の膜性能向上技術、透析方法が開発されてきた。それらに使用される膜素材としてはセルロース、セルロース誘導体などの天然素材とポリスルホン系、ポリメチルメタクリレート、ポリアクリロニトリル、エチレンビニルアルコール共重合体などの合成高分子素材が幅広く使用されている。合成高分子素材の中では、生体適合性に優れ、尿毒症物質の高い除去性能を発現しうるポリスルホン系樹脂が注目され、近年、ポリスルホン系樹脂を用いた血液浄化用膜が多数上市されている。ポリスルホン系樹脂は、熱可塑性の耐熱性エンジニアプラスチックであり、各産業分野において幅広く用途展開されている。

【０００３】ポリスルホン系樹脂は比較的疎水性が強く、血液と接触した際に、血漿タンパク質を吸着しやすい。このため血液浄化膜を作製する際に、血液との親和性を高めるために、ポリスルホン系樹脂にポリビニルピロリドンを混ぜることにより親水性を付与する方法が一般的に用いられている。

【０００４】親水性高分子、特にポリビニルピロリドンを含む選択分離膜を用いた血液透析治療中に、ポリビニルピロリドンの溶出に起因すると考えられるアナフィラキシーショック等の重篤な副作用が発生することが知られている。また、ドイツにおいては、Ｋ－１８（重量平均分子量１００００）以上のポリビニルピロリドンを静注することはできないとの規制がある。さらに、ポリビニルピロリドンを静注することによりアナフィラキシー症状を示すことが報告されている(Pilar Maiques Asuero ら、The Annals of Pharmacotherapy, pp30, January, Vol.30, 1996)。すなわち、ポリスルホン系樹脂膜の親水化剤として、一般に用いられているポリビニルピロリドンは安全性に問題があり、血液浄化用途に用いる際には、血液へのポリビニルピロリドンの溶出をできる限り抑える必要がある。

【０００５】ポリビニルピロリドンの溶出を抑えるために、これまで多くの方法が提案されている。例えば、特開平１０－２３０１４８には、ポリビニルピロリドンを含むポリスルホン系中空糸膜を熱処理あるいは放射線処理を施すことにより、ポリビニルピロリドンを架橋し、不溶化することでポリビニルピロリドンの溶出を抑える方法が開示されている。また、特開平１０－２４３９９９には、選択分離層の厚みを適切にすることで、ポリビニルピロリドンの溶出を抑える方法が開示されている。しかしながら、これらの手法は、ある程度は熱水への溶出量抑制に対しては効果があるものの、後述するように、血液あるいは血漿への溶出量の指標となる４０％エタノール水溶液への溶出量抑制には不十分である。実際、ポリビニルピロリドンの溶出量を抑制したといわれる透析膜においても、未だ、アナフィラキシーショック発生の報告があり（例えば、中山ら、0-439 、第43回日本透析医学会予稿集、pp620 、 1998 ）、ポリビニルピロリドンを含有する選択分離膜の安全性に対する問題は解決していないのが現状である。

【０００６】

【発明が解決しようとする課題】本発明は、上記課題を解決することを目的とし、生体内において異物と認識される親水性高分子が溶出しにくい選択分離膜を提供することを目的とする。

【０００７】

【課題を解決するための手段】本研究者らは、上記課題を解決し、優れた安全性を具備する選択分離膜を提供するため鋭意研究した結果、本発明に到達した。すなわち本発明は、以下のものである。

①　疎水性高分子と親水性高分子からなる選択分離膜において、40% エタノール水溶液で抽出される該親水性高分子が選択分離膜の被処理液接触側膜面積1m^2 あたり10mg以下であることを特徴とする選択分離膜。

②　被処理液が血液である上記①記載の選択分離膜。

③　血液透析用、血液透析濾過用、血液濾過用、血漿分離用、血漿分画用または腹水濃縮用に用いる上記①または②記載の選択分離膜。

④　選択分離膜が中空糸膜である上記①乃至③記載の選択分離膜。

⑤　疎水性高分子がポリスルホン系樹脂である上記①乃至④記載の選択分離膜。

⑥ 親水性高分子がポリビニルピロリドンである上記①乃至⑤記載の選択分離膜。

【０００８】本発明において、４０％エタノール水溶液で抽出される親水性高分子が、選択分離膜の被処理液側膜面積１m^2 あたり１０ｍｇ以下であるのは、次の理由による。まず、疎水性高分子と親水性高分子からなる選択分離膜において、該親水性高分子の溶出を皆無にすることは不可能であるので安全性の上限を決める必要があった。溶出するポリビニルピロリドンに対する、アレルギー反応は人によって異なるが、我々がビーグル犬を用いてポリビニルピロリドンを静注したときのアナフィラキシー反応を調べたところ、体重１Ｋｇ当たり５ｍｇのポリビニルピロリドンの静注まではアナフィラキシー反応を起こさないことがわかった。人の固体差を加味しビーグル犬の安全投与量の１／１０を上限とし、また通常血液透析に用いられる透析器の膜面積の上限が約２m^2 であること、透析患者の体重の下限を４０ｋｇとすると、１透析当たり２０ｍｇがポリビニルピロリドンの投与上限であり、１m^2 当たり１０ｍｇ以下とすることで安全性が確保できると考えられる。

【０００９】実際、我々が現在市販されているポリビニルピロリドンを含有するポリスルホン系透析膜の４０％エタノール水溶液での抽出試験によるポリビニルピロリドンの溶出量を測定したところ、１m^2 あたり数ｔｍｇ～数百ｍｇの溶出があることがわかった。そのため、ポリビニルピロリドンを含有するポリスルホン系膜の安全性を確保するためには、これらの事実により１m^2 当たり１０ｍｇ以下の溶出量に抑えることで達成できる。

【００１０】また、我々が４０％エタノール水溶液による抽出を選択した理由は以下による。すなわち、血液浄化の目的で選択分離膜を使用する場合、被処理液は水ではなく、血液あるいは血漿である。血液あるいは血漿は、水に電解質や血漿タンパク質、血球、その他の有機成分を含むので、各種溶質に対する溶解力は水や熱水に比べかなり高いといわれている。４０％エタノール水溶液による抽出は、血液回路に用いられる塩化ビニルの添加剤（フタル酸エステル）の抽出量の測定に使用され、水や熱水に比べ、より血液に近い抽出力を持つといわれている。この４０％エタノール水溶液を用いることによってポリビニルピロリドンを含有する選択分離膜の血液接触時のポリビニルピロリドンの溶出量を測定できると考えた。

【００１１】実際、我々が現在、市販されている、ポリビニルピロリドンを含有する選択分離膜のポリビニルピロリドン溶出量を他の条件は同一として、７０℃純水と４０％エタノール水溶液で比較したところ、４０％エタノール水溶液による抽出量は７０℃純水の抽出量の５～２０倍となることがわかった。

【００１２】以上の研究により、４０％エタノール水溶液で抽出される該親水性高分子が、該選択分離膜の被処理液側膜面積１m^2 当たり１０ｍｇ以下にすることにより、安全性が著しく向上した選択分離膜が得られることを見出し、本発明に到達した。

【００１３】本発明において、被処理液とは、選択分離膜によって分離対象となる液体をいい、被処理液接触側とは、膜の被処理液が接触する側の表面をいう。すなわち、血液透析や血液濾過、血液透析濾過、血漿分離においては、被処理液は血液であり，血漿分画においては被処理液は血漿であり、この場合被処理液接触側とは、膜の血液（血漿分画の場合は血漿）接触面をいう。中空糸形状の選択分離膜を血液浄化用途に用いた場合、被処理液接触側とは通常、中空糸内側である。血液透析や血液透析濾過においては、膜の片側に血液を、反対側に透析液を流すが、膜から被処理液へ親水性高分子の溶出を抑えることにより安全性を向上する目的から明らかなように、このような場合、本発明において被処理液は血液あるいは血液成分であって、透析液ではない。

【００１４】また、本発明は、血液浄化の他、親水性高分子が溶出することで不都合が生じる用途、例えば、食品や飲料、生理活性物質の濃縮や精製等に好適に利用でき、被処理液としては食品、飲料、生理活性物質含有液体等を挙げることができるが、被処理液を再び人体に戻す血液浄化用途に本発明を応用すれば、安全性が向上するため、血液あるいは血液の成分を被処理液として用いた場合に、本発明は最も効果的である。本発明の選択分離膜は、上述のように処理後の血液を人体に戻す血液浄化用途に応用することが好ましく、具体的には血液透析膜、血液透析濾過膜、血液濾過膜、血漿分離膜、血漿分画膜、腹水濃縮膜などが挙げられる。本発明の選択分離膜のとりうる形態としては、平膜、管状膜、中空糸膜等が挙げられるが、単位容積あたりの膜面積を大きくとれる中空糸膜が好ましい。

【００１５】本発明における疎水性高分子とはポリエステル、ポリカーボネート、ポリウレタン、ポリアミド、ポリスルホン、ポリエーテルスルホン、ポリメチルメタクリレートなどの合成高分子やセルローストリアセテート、セルロースナイトレート等のセルロース系素材があり、特に限定されるものではないが、ポリスルホン、ポリエーテルスルホン等のポリスルホン系素材は、血液浄化に用いた際，生体適合性に優れ、尿毒症物質の高い除去性能が得られるので好ましい。また、これらは単独で用いても２種以上を混合して用いても良い。

【００１６】本発明における親水性高分子とはポリエチレングリコール、ポリビニルアルコール、ポリビニルピロリドン、カルボキシメチルセルロース、デンプンおよびその誘導体、酢酸セルロースなどの素材であるが、ポリスルホン系樹脂との相溶性を有することから好ましいのはポリビニルピロリドンである。

【００１７】本発明の実施形態としては、親水性高分子の分子量が最も重要である。ポリスルホン系樹脂とポリ

ビニルピロリドンからなる膜において、ポリビニルピロリドンは、ポリスルホン系樹脂に取り囲まれて存在していると考えられる。そのため、親水性高分子の分子量を大きくすることで、膜中から抜け落ちにくくなる。ポリビニルピロリドンは分子量の異なるグレードが市販されており、最も分子量が大きいグレード（K-90）は、数平均分子量が約３６万程度であり、この程度の分子量のポリビニルピロリドンは、膜中から抜け落ちることは考えにくい。しかし、市販のポリビニルピロリドン分子量分布を有しており、分子量数万～10万程度の分子が多量に含まれている。われわれの検討結果では、K-90を使用して作製されたポリスルホン系樹脂膜の４０％エタノール水溶液での抽出実験により、溶出してくるポリビニルピロリドンをゲルパーミエーションクロマトグラフィーにて測定したところ、その分子量は２～５万程度であり、10万以上の分子量のポリビニルピロリドンはほとんど検出されなかった。すなわち、クロマトグラフ法や再沈殿法など方法は問わないが、市販のポリビニルピロリドンK-90に処置を施し、低分子量体を積極的に除去し、これを中空糸膜製膜する際に使用することによって、４０％エタノール水溶液抽出によるポリビニルピロリドンの溶出を、被処理液接触側膜面積$1m^2$あたり10mg以下に抑えることが可能になる。除去される低分子量体は通常分子量５万未満、好ましくは１０万未満である。

【００１８】以下実施例により本発明の詳細を示す。

【００１９】４０％エタノール抽出試験は以下のような手順で行った。中空糸膜モジュールの中空糸内側（被処理液側）に４００ｍＬの純水を流してフラッシング作業を行った後、モジュール内の純水を４０vol %エタノール水溶液で中空糸内側を置換した。中空糸外側のモジュールケース内も４０vol %エタノールで満たして封止した。次に２００ｍＬの４０vol %エタノール水溶液を、流量１５０ｍＬ／ｍｉｎ、４０℃、１時間中空糸内側を循環させた後、循環した４０vol %エタノール水溶液中のポリビニルピロリドン濃度を測定した。モジュールの中空糸内側容積とモジュール入口出口のヘッダー部分の体積、すなわちプライミングボリュームに２００mL を加えた、抽出液総体積と抽出液中のポリビニルピロリドン濃度から、抽出されたポリビニルピロリドン重量を求め、さらに、中空糸膜モジュールの膜面積（中空糸内径基準）から、被処理液接触側膜面積$1m^2$あたりのポリビニルピロリドン抽出量を求める。

【００２０】ポリビニルピロリドンの濃度測定にはK. Mueller （１９６８）の方法を用いた。すなわち、検体にクエン酸とヨウ素液を加え、吸光度を測定し、ポリビニルピロリドンK-90から求めた検量線により濃度を求めた。ここで濃度測定の際、エタノールによる発色の阻害をなくすために２倍以上に希釈する必要がある。具体的には例えば２倍希釈であれば、検体（標品あるいは抽出液）を１．２５mL、水１．２５mL、０．２Mクエン酸水溶液１．２５mL、０．００６Ｎヨウ素水溶液０．５mLをよく混合し、１０分静置した後、４７０nmでの吸光度を測定し、ポリビニルピロリドンの濃度を測定した。

【００２１】

【実施例】

【００２２】実施例１

ポリビニルピロリドン（Ｋ－９０，BASF社製）0.025g/mLの水溶液を、水溶液の水に対する溶比が2.5 ～3.0 倍の貧溶媒であるアセトン中へ滴下し、再沈殿法により積極的に低分子量体を除去したポリビニルピロリドンを収率90% で得た。これを以下、精製ポリビニルピロリドンと称する。精製前のポリビニルピロリドンと、精製時に排除した分画のゲルパーミエーションクロマトグラフィーのプロファイルを図１、図２に示す。図より明らかなように、精製時に低分子分画（透過時間が長い方向）のみが選択的に排除されていることがわかる。ポリエーテルスルホン（４８００Ｐ、住友化学社製）１６重量部と精製ポリビニルピロリドン５重量部をジメチルアセトアミド７４重量部、水５重量部を混合溶解、脱泡した紡糸原液として、５０％ジメチルアセトアミド水溶液を芯液として使用し、これを二重管オリフィスより吐出し、５０ｃｍの空走部を経て、７５℃、水の凝固浴中に導き中空糸膜を形成し、水洗後まきとり、６０℃で２０ｈｒ乾燥した。この中空糸膜を使用して中空糸内径基準膜面積１．５m^2のモジュールを得た。このモジュールで４０％エタノール抽出試験を行った結果、ポリビニルピロリドンの溶出は中空糸内膜面積$1m^2$ あたり１．０ｍｇであった。

【００２３】実施例２

ポリスルホン（Ｐ－１７００、AMOCO社製）２０重量部、精製ポリビニルピロリドン６重量部、ジメチルアセトアミド７４重量部を混合溶解、脱泡した紡糸原液として、４５％ジメチルアセトアミド水溶液を芯液として使用し、これを二重管オリフィスより吐出し、７０ｃｍの空走部を経て、５０℃、水の凝固浴中に導き中空糸膜を形成し、水洗後まきとり、６０℃で２０ｈｒ乾燥した。この中空糸を使用して中空糸内径基準膜面積１．５m^2のモジュールを得た。このモジュールで４０％エタノール抽出試験を行った結果、ポリビニルピロリドンの溶出は中空糸内膜面積$1m^2$ あたり１．３ｍｇであった。

【００２４】比較例

ポリビニルピロリドンとして精製していないＫ－９０（BASF社製）を用いた以外は実施例２と同様に、中空糸膜を紡糸し、得られた中空糸を使用して中空糸内径基準膜面積１．５m^2のモジュールを得た。このモジュールで４０％エタノール抽出試験を行った結果、ポリビニルピロリドンの溶出は中空糸内膜面積$1m^2$ あたり１５．２ｍｇであった。

【００２５】

【表１】

	実施例１	実施例２	比較例
親水性高分子の溶出量(mg)	１．０	１．３	１５．２

【００２６】

【発明の効果】本発明により、親水性高分子を含有するが、該親水性高分子の溶出が少ない選択分離膜を提供することができた。

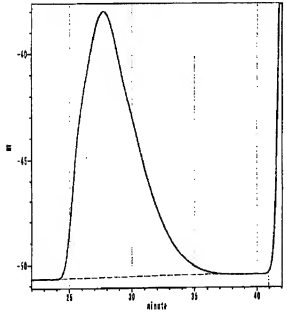
【図面の簡単な説明】

【図１】ポリビニルピロリドン（Ｋ－９０）のゲルパーミエーションクロマトグラフィーのプロファイルを示す。

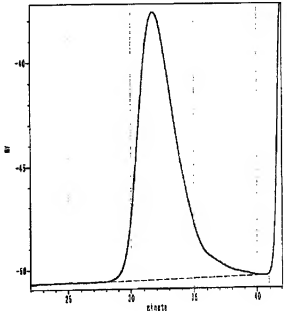
【図２】ポリビニルピロリドン精製時に排除した分画のゲルパーミエーションクロマトグラフィーのプロファイルを示す。

【図３】４０%エタノール抽出により溶出が検出されたポリビニルピロリドンのゲルパーミエーションクロマトグラフィーのプロファイルを示す。

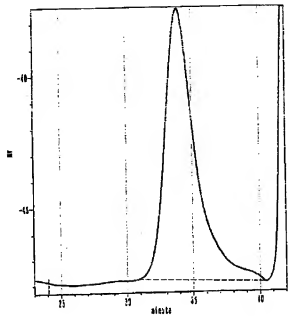
【図１】



【図２】



【図３】



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